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CME

Recovery of Platelet Function After Discontinuation of Prasugrel or Clopidogrel Maintenance Dosing in Aspirin-Treated Patients With Stable Coronary Disease

The Recovery Trial

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to assess the ofset of the antiplatelet effects of prasugrel and clopidogrel.

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Recovery of Platelet Function After Discontinuation of Prasugrel or Clopidogrel Maintenance Dosing in Aspirin-Treated Patients With Stable Coronary Disease

The Recovery Trial

Objectives The goal of this study was to assess the offset of the antiplatelet effects of prasugrel and clopidogrel.

Background Guidelines recommend discontinuing clopidogrel at least 5 days and prasugrel at least 7 days before surgery. The pharmacodynamic basis for these recommendations is limited.

Methods Aspirin-treated patients with coronary artery disease were randomly assigned to either prasugrel 10 mg or clopidogrel 75 mg daily for 7 days. Platelet reactivity was measured before study drug administration and for up to 12 days during washout. The primary endpoint was the cumulative proportion of patients returning to baseline reactivity after study drug discontinuation.

Results A total of 56 patients were randomized; 54 were eligible for analysis. Platelet reactivity was lower 24 h after the last dose of prasugrel compared with clopidogrel. After prasugrel, ≥75% of patients returned to baseline reactivity by washout day 7 compared with day 5 after clopidogrel. Recovery time was dependent on the level of platelet reactivity before study drug exposure and the initial degree of platelet inhibition after study drug discontinuation but not on treatment assignment.

Conclusions Recovery time after thienopyridine discontinuation depends on the magnitude of on-treatment platelet inhibition, resulting, on average, in a more delayed recovery with prasugrel compared with clopidogrel. The offset of prasugrel was consistent with current guidelines regarding the recommended waiting period for surgery after discontinuation. (Prasugrel/Clopidogrel Maintenance Dose Washout Study; NCT01014624) (J Am Coll Cardiol 2012;59:2338–43) © 2012 by the American College of Cardiology Foundation

Thienopyridines are prodrugs that require biotransformation into an active metabolite that irreversibly antagonizes the $P2Y_{12}$ receptor for the platelet's lifespan. A prasugrel 60-mg loading dose and 10-mg daily maintenance dose (MD) provide greater and more consistent levels of platelet inhibition than clopidogrel due to more efficient active metabolite generation (1,2). Clopidogrel use before cardiac surgery increases bleeding (3,4). In the 437 patients who underwent coronary artery bypass graft (CABG) in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, more bleeding occurred with prasugrel compared with clopidogrel up to 1 week after discontinuation (5). Based on these clinical observations, the American College of Cardiology/American Heart Association guidelines recommend empirical discontinuation of clopidogrel for at least 5 days and prasugrel for at least 7 days before planned CABG, unless the net benefit of the thienopyridine outweighs the potential risks of excess bleeding (6). However, the dynamics of platelet functional recovery after prasugrel cessation have not been specifically assessed. Therefore, we performed this study to examine the relationship between the timing of drug discontinuation and the recovery of platelet function after prasugrel compared with clopidogrel therapy.

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Methods

Study design. This trial was a randomized, double-blinded study conducted at 4 sites in the United States. The study was approved by the institutional review boards at all sites and was conducted in accord with the provisions of the Declaration of Helsinki. All subjects provided written informed consent.

Study population. Subjects were eligible to be enrolled if they were <75 years of age, had stable coronary artery disease (CAD), and were receiving aspirin. Detailed inclusion and exclusion criteria and participating sites are listed in the Online Appendix.

Study procedures. Patients were randomly assigned 1:1 to prasugrel 10 mg or clopidogrel 75 mg daily for 7 days. Patients returned over the course of the washout period for platelet function assessment (Fig. 1). Randomization and visit details are provided in the Online Appendix. Patients were considered to have completed the study when platelet function returned to baseline according to the primary and

Abbreviations and Acronyms

CABG = coronary artery bypass graft

CAD = coronary artery disease

IPA = inhibition of platelet aggregation

MD = maintenance dose

PRU = P2Y12 reaction units

secondary definitions or at the end of the 12-day washout period if platelet function did not return to baseline.

Platelet function measurement. Platelet function was assessed by using the VerifyNow P2Y12 test (Accumetrics, San Diego, California), which measures adenosine diphosphate–induced platelet aggregation as an increase in light transmittance and reports values in PRU (7). A higher PRU reflects greater platelet reactivity.

Genetic methodology. Genotyping for *CYP2C19**2,*3, and *17 was performed by using TaqMan assays. CYP2C19 metabolizer phenotype was categorized as either extensive or reduced, as previously described (8).

Definitions and endpoints. The primary endpoint of the trial was the return to baseline platelet function after study drug discontinuation. Return to baseline was defined as platelet reactivity within 60 PRU of reactivity before study drug administration. This window is within 1 SD of baseline reactivity measured by using the VerifyNow P2Y12 test in a previous study of patients with stable CAD (7). Analyses were also performed with a secondary definition of return to baseline: inhibition of platelet aggregation (IPA), defined as: $[(PRU_{pre\text{-}study\ drug} - PRU)/(PRU_{pre\text{-}study\ drug}) \times 100]$, ≤20%. High residual platelet reactivity was defined as >230 PRU (9).

The main objective was to describe the primary endpoint over the washout period. Secondary objectives were to: 1) determine the day at which ≥50%, ≥75%, and ≥90% of patients returned to baseline platelet function; 2) determine the day at which the proportion of prasugrel-treated patients who had returned to baseline function was closest to the proportion of clopidogrel-treated patients who had returned to baseline function at washout days 5 and 7; and 3) examine the relationship between IPA 24 h after the last dose of study drug and the number of days required to return to baseline function.

Statistical analysis. The analysis population was defined as all patients who had completed the study drug phase and had platelet function data available at baseline and 24 h after study drug discontinuation. The safety population was defined as all patients who received at least 1 dose of study drug. Kaplan-Meier analysis was used to estimate the proportion of patients who returned to baseline platelet function over time. Multivariate regression of the pooled treatment groups was performed to determine variables independently associated with the primary endpoint. Details of this analysis and the sample size calculation are described in the Online Appendix.

Results

Study flow is shown in Figure 2. A total of 56 patients were randomized and received at least 1 dose of study drug; 54 were included in the analysis population, and 53 completed the study visits. Patient demographic and clinical characteristics, as well as concomitant medication use, are shown in Table 1.

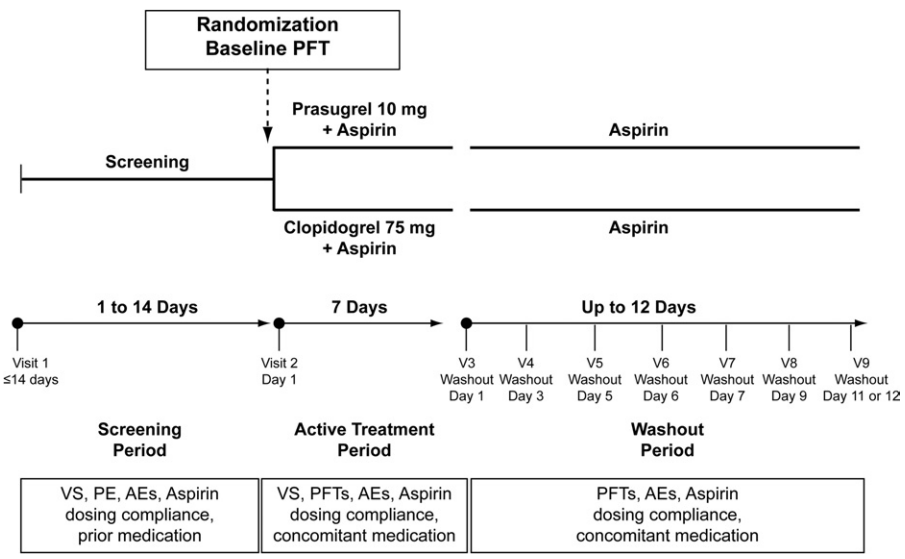

Figure 1 Trial Design

Patients were randomly assigned to either prasugrel 10 mg daily or clopidogrel 75 mg daily for 7 days, at which time study drug was discontinued. Patients then returned over the washout period for platelet function assessment. AE = adverse event; PE = physical examination; PFT = platelet function test; V = visit; VS = vital signs.

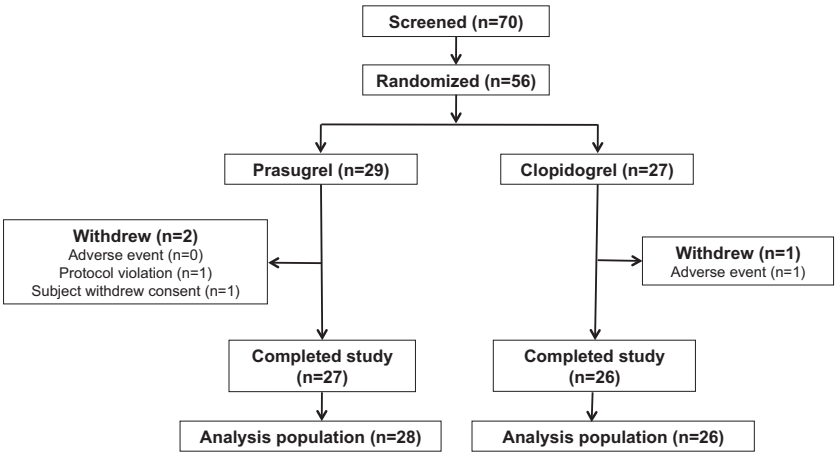

Figure 2 Study Flow

Fifty-six patients were randomized and received at least 1 dose of study drug, representing the safety population. Fifty-four patients completed the study drug phase and had, at a minimum, platelet function data before study drug administration and at 24 hours after discontinuation, representing the analysis population.

Platelet function over time. Pre-treatment platelet reactivity was 285 ± 46 PRU and 298 ± 47 PRU among the patients randomly assigned to receive prasugrel and clopidogrel, respectively. Residual platelet reactivity was lower 24 hours after the last dose of prasugrel compared with clopidogrel (78 ± 36 PRU vs. 196 ± 81 PRU); IPA was 72 ± 12% after prasugrel administration compared with 35 ± 23% after clopidogrel administration (Fig. 3). No patients assigned to prasugrel and 11 patients (42%) assigned to clopidogrel displayed high residual platelet reactivity.

Figure 4 shows the cumulative proportion of patients returning to baseline platelet reactivity over the washout period. In the prasugrel group, ≥50% of patients returned to baseline reactivity by washout day 6, ≥75% by day 7, and ≥90% by day 9; in the clopidogrel group, ≥50% of patients

Table 1 Baseline Characteristics of the Study Population

Characteristic	Prasugrel (n = 29)	Clopidogrel (n = 27)	Total (N = 56)
Age (yrs)	57.5 ± 8.45	62.3 ± 8.10	59.8 ± 8.56
Male	25 (86.2)	20 (74.1)	45 (80.4)
Body mass index (kg/m^2)	32.0 ± 4.07	30.3 ± 5.34	31.2 ± 4.76
Current smoker*	6 (20.7)	5 (18.5)	11 (19.6)
Diabetes mellitus	11 (37.9)	11 (40.7)	22 (39.3)
Hypertension	22 (75.9)	17 (63.0)	39 (69.6)
Hyperlipidemia	28 (96.6)	26 (96.3)	54 (96.4)
CYP2C19 phenotype			
Extensive metabolizer	25 (86.2)	23 (85.2)	48 (85.7)
Reduced metabolizer	4 (13.8)	3 (11.1)	7 (12.5)
Unavailable	0 (0)	1 (3.7)	1 (1.8)
Prior medication use			
Aspirin	29 (100)	27 (100)	56 (100)
Aspirin 81 mg daily	23 (79.3)	18 (66.7)	44 (73.2)
Proton pump inhibitors	3 (10.3)	1 (3.7)	4 (7.1)
Dihydropyridine calcium-channel blocker	4 (13.8)	3 (11.1)	7 (12.5)
Non-dihydropyridine calcium-channel blocker	0 (0)	1 (3.7)	1 (1.8)
Beta-blocker	15 (51.7)	14 (51.9)	29 (51.8)
HMG-CoA reductase inhibitor	25 (86.2)	20 (74.1)	45 (80.4)
ACE inhibitor	14 (48.3)	12 (44.4)	26 (46.4)

Values are mean ± SD or n (%). *Current smoker ≥10 cigarettes per day.
ACE = angiotensin-converting enzyme; CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

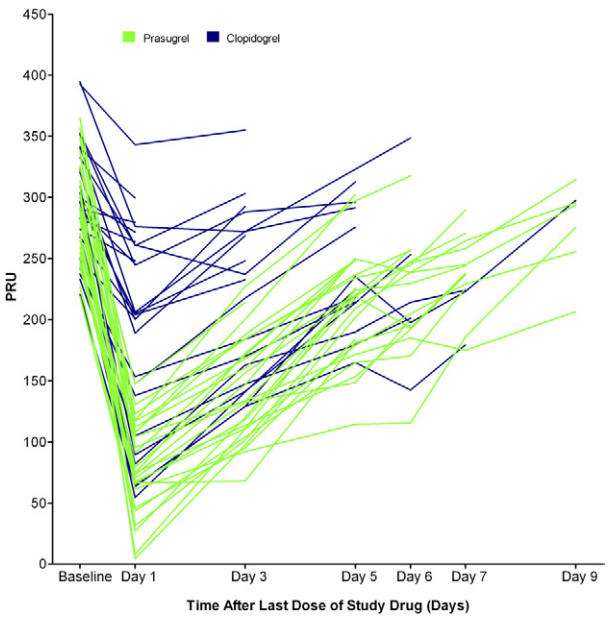

Figure 3 Residual Platelet Reactivity Over Time by Individual Patient and Study Group Assignment

The initial magnitude of platelet inhibition at discontinuation was an independent predictor of the time to recovery, resulting, on average, in a more prolonged recovery after prasugrel. PRU = P2Y12 reaction units.

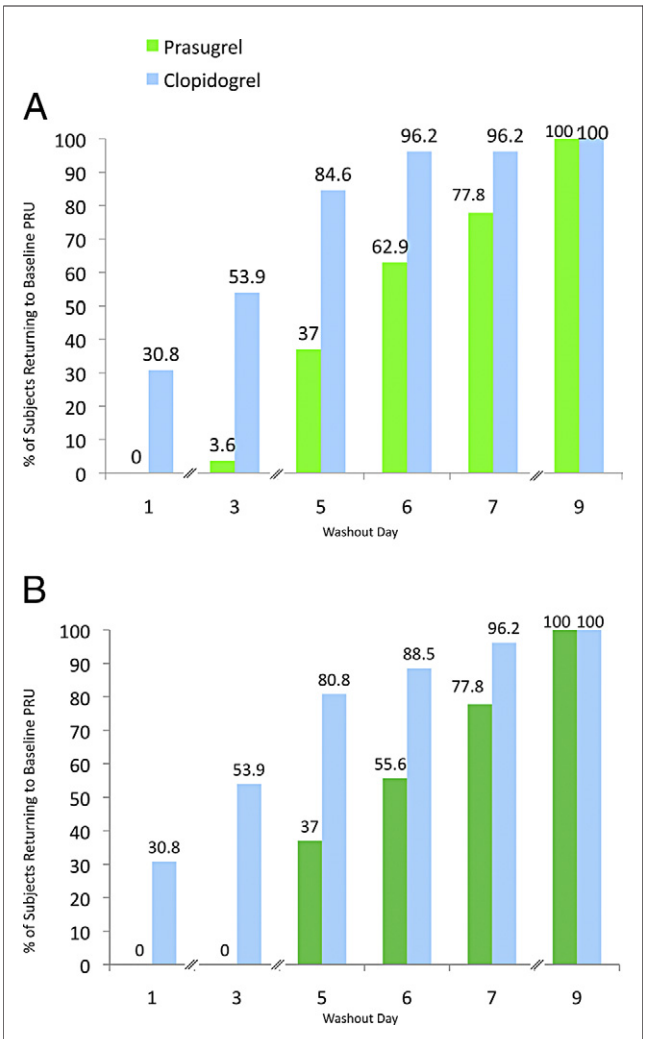

Figure 4 Cumulative Proportion of Patients Returning to Baseline Reactivity After Thienopyridine Discontinuation

(A) Baseline platelet reactivity defined as within 60 PRU of the reactivity measured before study drug exposure and **(B)** baseline platelet function defined as inhibition of platelet aggregation ≤20%. PRU = P2Y12 reaction units.

returned to baseline reactivity by washout day 3, ≥75% by day 5, and ≥90% by day 6. Washout day 7 was the day at which the proportion of prasugrel-treated patients who had returned to baseline reactivity was closest to the proportion attained by the clopidogrel-treated group at washout day 5 (22 [78%] vs. 22 patients [85%], respectively). Similar findings were observed using the definition of return to baseline as <20% IPA, except 90% of patients in the clopidogrel group had recovered by washout day 7 rather than day 6.

Predictors of recovery time. According to multivariate analysis, the level of platelet reactivity before study drug exposure and the IPA 24 h after study drug discontinuation were independently associated with the number of days to the return to baseline platelet function ($p < 0.0001$ for both; adjusted R^2 for final model = 0.72). Treatment assignment was not associated with recovery time after adjusting for these variables.

Safety. Ten patients in the prasugrel group and 5 in the clopidogrel group experienced treatment-emergent adverse events; none was serious. The adverse events were considered study drug–related in 4 prasugrel-treated patients and 2 clopidogrel-treated patients (Table 2). No bleeding events were reported although 2 prasugrel-treated patients experienced an increased tendency to bruise. One clopidogrel-treated patient and no prasugrel-treated patients discontinued study drug due to an adverse event.

Discussion

Surgical bleeding is significantly increased during and after thienopyridine therapy. These observations, together with the irreversible antagonism of the platelet $P2Y_{12}$ receptor provided by these agents, has led to empirical recommendations for the optimal waiting period for surgery after thienopyridine discontinuation (6). In this study, we found that in aspirin-treated patients with CAD, the time to platelet functional recovery after thienopyridine MD depended on the level of platelet reactivity before study drug exposure and the initial magnitude of platelet inhibition after discontinuation. Therefore, the greater antiplatelet effect of prasugrel resulted, on average, in a more delayed recovery of platelet function compared with clopidogrel. Furthermore, we observed that a waiting period of 7 days after prasugrel cessation provided a degree of recovery closest to the 5-day waiting period for clopidogrel, at which point the antiplatelet effects of both agents had dissipated in ≥75% of patients. Our findings are consistent with, and provide pharmacodynamic support for, current guidelines regarding the recommended waiting time for surgery after prasugrel discontinuation (6).

Rates of major bleeding, blood transfusions, reoperation, and lengths of stay are increased among patients undergoing CABG ≤5 days of last exposure to clopidogrel (3,4). Among patients who underwent CABG in the TRITON-TIMI 38 trial, the rate of CABG-related bleeding was significantly greater with prasugrel compared with clopidogrel, and this increased risk persisted up to 7 days from the most recent dose of study drug (5). We observed that most clopidogrel-treated patients recovered platelet function by 5 days after drug cessation, and the proportion of prasugrel-treated patients who recovered platelet function was most similar to this time point at 7 days after cessation. The lack of an increased bleeding risk in clinical studies after a 5- and 7-day waiting period with clopidogrel and prasugrel, respectively, is consistent with our

Table 2 Subjects With Drug-Related Treatment-Emergent Adverse Events in the Safety Population*

Adverse Event	Prasugrel (n = 29)	Clopidogrel (n = 27)
Ecchymosis	0	1
Increased tendency to bruise	2	0
Epistaxis	2	0
Diarrhea	1	1
Diabetes mellitus	0	1
Insomnia	0	1

*Subjects may have experienced 1 or more event.

pharmacodynamic findings. Although most patients in the current study returned to baseline platelet reactivity after 5 and 7 days of clopidogrel and prasugrel discontinuation, respectively, patients in both groups displayed residual effects beyond these waiting periods. Because lower levels of adenosine diphosphate–induced platelet reactivity are associated with increased surgical bleeding (10), a longer waiting period (6 to 7 days for clopidogrel and 9 days for prasugrel) could be desirable to further mitigate any potential bleeding risk due to thienopyridine-induced platelet inhibition.

Our findings highlight the interindividual variability in the recovery time after clopidogrel exposure that is a direct consequence of clopidogrel response variability (9). In the current study, 87% of the patients randomly assigned to clopidogrel had fully recovered platelet function after the guideline-recommended 5-day waiting period. However, because the inhibitory response to clopidogrel was substantially variable, and functional recovery time was dependent on the initial magnitude of platelet inhibition, one-half of the clopidogrel-treated patients recovered platelet function by day 3 while several had persistent inhibition beyond 5 days. This observation is consistent with previous studies of platelet functional recovery after clopidogrel treatment (11). A uniform strategy of a 5-day waiting period after clopidogrel could expose patients with marginal response to thrombotic risk, while exposing "hyper-responders" to an increased surgical bleeding risk. Platelet function testing could help guide surgical timing in thienopyridine-treated patients to minimize bleeding complications, although the evidence supporting such an approach is limited by the lack of firm cutoffs to predict bleeding events.

Study limitations. We could not determine the mean levels of platelet reactivity or inhibition for the entire study population after the first washout visit because we did not collect platelet function data after subjects' platelet reactivity returned to baseline according to the protocol definition. We assessed platelet function solely by using the VerifyNow P2Y12 test. The small sample size may have limited our ability to detect the influence of *CYP2C19* and other clinical variables. We did not assess clinical outcomes post-surgery and therefore could not directly correlate pharmacodynamics with surgical bleeding. The distribution of aspirin dose differed by chance between treatment groups; however, the consistent aspirin exposure for each patient throughout the course of the study diminished the likelihood of this imbalance affecting the study findings.

Conclusions

In aspirin-treated patients with stable CAD, the antiplatelet effects of prasugrel 10 mg MD were greater than those of clopidogrel 75 mg MD. After discontinuation, the proportion of patients who recovered platelet function on day 5 of clopidogrel was similar to day 7 of prasugrel. The initial magnitude of platelet inhibition at discontinuation was an independent predictor of the time to recovery, resulting, on average, in a more prolonged recovery after prasugrel. Our findings are consistent with current guidelines and product labeling regarding the recommended waiting time for surgery after discontinuation of prasugrel.

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Key Words: bleeding ■ clopidogrel ■ platelet function ■ prasugrel ■ surgery ■ thienopyridine.

APPENDIX

For supplementary details regarding the study protocol, please see the online version of this article.